Incidence and Follow-Up of Inflammatory Cardiac Complications after Smallpox Vaccination in a Large Cohort of Healthy Vaccinees

Eckart RE, Atwood JE, Grabenstein JD

Love SS, Riddle JR, Arness MK, Engler RJ

for the Department of Defense Smallpox Vaccination Clinical Evaluation Team

Methods

- Case Identification
  - DMSS, active solicitation, publications (MMWR, JAMA), VAERS
  - 76 cases identified, 67 cases with data made available for review >60 days since diagnosis used as cohort for this presentation
- Data collated and centralized by the VHC
- Clinical Follow-up Protocol
  - Guidelines for follow-up developed through working groups facilitated by VHC and MilVax
  - Distributed to providers June 9, 2003
  - Clinical evaluation, labs, ECG, echo, and GXT at 6-12 weeks
  - Patients with persistent symptoms could be transferred to regional MTF for further evaluation
  - http://www.smallpox.mil/media/pdf/algorhythm.pdf

Demographics

Age, years	26.6±5.2 (18.8-43.0)
Ethnicity	
Caucasian	60 (89.5%)
African-American	4 (6.0%)
Hispanic	2 (3.0%)
Asian	1 (1.5%)
Gender	
Male	66 (98.5%)
Female	1 (1.5%)
Vaccination to evaluation, days	
Mean±SD	10.4±3.6
Median (range)	10 (3-25)
Time to follow-up, weeks	
Mean+/-SD	31.5±15.2
Median (range)	32.7 (1.6-58.1)

Continuous variables expressed as mean±SD (range). Categorical variables expressed as raw data (percent of column total).

Presentation

- All 67 cases presented initially with chest pain
- Prodromal symptoms documented in 61 (91.1%)
  - 35 (57%) fever and chills
  - 19 (31%) myalgias and/or arthralgias
  - 26 (34%) headache, “viral syndrome” and fatigue
  - 9 (15%) no prodromal syndrome until chest pain prompted medical evaluation

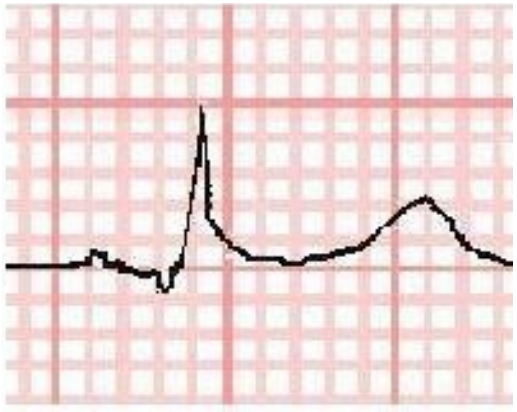
Follow-up

- Data available on 64 (96%) patients
  - Two patients self-reported as healthy but voluntarily separated from military service and declined to return for follow-up
  - One patient died during hospitalization
    - Unlike other cases, had normal cardiac enzymes 15 and 28 days post-vaccination, prolonged pulmonary condition, elevated enzymes 32 post vaccination
  - mean of 32±15 weeks after presentation

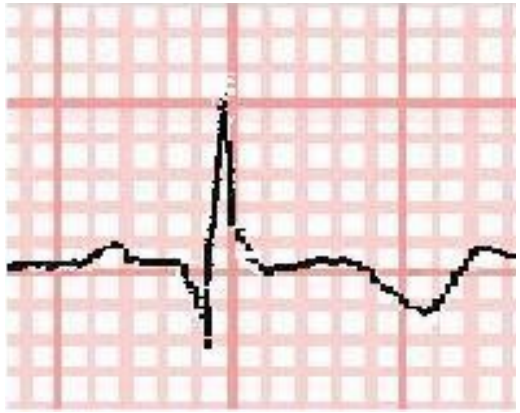
Electrocardiography

- Initial tracing available for review in 61 (91.0%)
- Identifiable abnormality in 46 (75.4%)
  - ST-segment abnormality in 40 patients
    - 35 (57.4%) pathologic ST-segment elevation
    - 5 (8.2%) had normal variant early repolarization
  - T-wave abnormality in 11 (18.0%)
- 44 had follow-up available for review (72.1%)
  - 20-120 days (median 97 days) from initial presentation
  - Normalization of pathologic ST-segment elevation and T-wave inversions in all patients

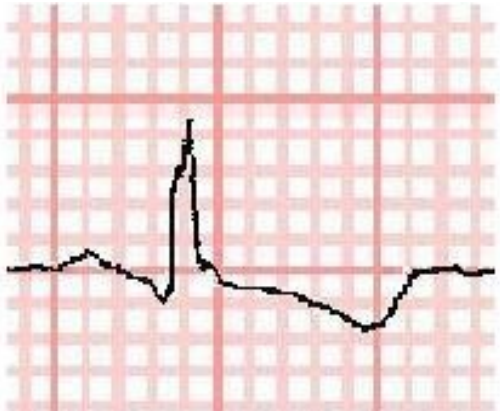
Electrocardiography



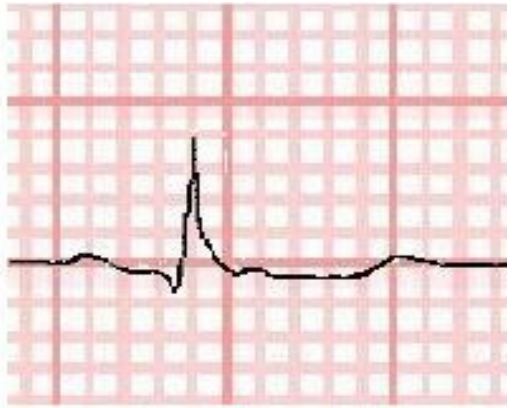
Week 1



Week 2

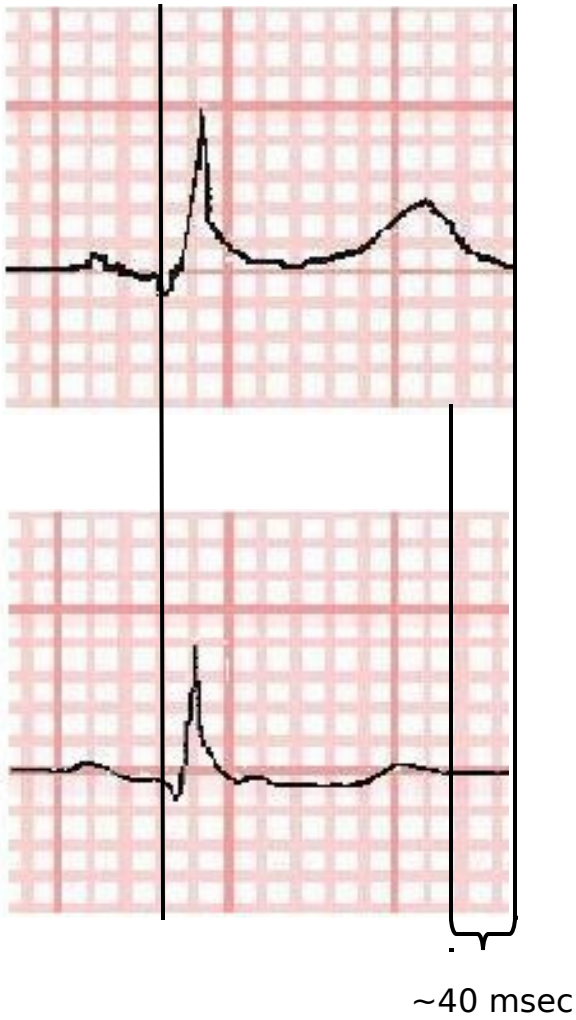


Week 4



Week 10

Electrocardiography



- Ventricular repolarization heterogeneity has been associated with risk of sudden death, and normalization has been associated with decreased risk
  - Interlead $QT_{c\text{-}d}$, at baseline vs. follow-up 67±27 vs. 22±23 msec, $p<0.001$ (95% CI 35-59 msec)
  - Proven stabilization of ventricular repolarization using $QT_{c\text{-}d}$ as a surrogate measure.
  - In other cardiac pathology, normalization of repolarization may be associated with decreased inflammation.
- All follow-up ECGs had normal parameters for ventricular

Electrocardiography

	Presentation	Follow-up
Sinus rhythm	61 (100.0%)	41 (100.0%)
Heart rate, beats per minute	74±17	74±14
PR interval, msec	150±22	150±24
QRS duration, msec	90±9	91±9
QT interval, msec	373±43	378±27
Pathologic ST-elevation*	35 (57.4%)	0 (0.0%)
Systolic blood pressure, mmHg	114±11	121±13
Diastolic blood pressure, mmHg	73±8	73±10

*$p<0.01$, otherwise $p>0.05$ for all comparisons; msec=milliseconds. Continuous variables expressed as mean±SD. Categorical variables expressed as raw data (percentage of column total). Pathologic ECG changes were defined as a new finding of ST-segment elevation $\geq$ 1 mm (0.1 mV) elevation in 2 or more contiguous leads

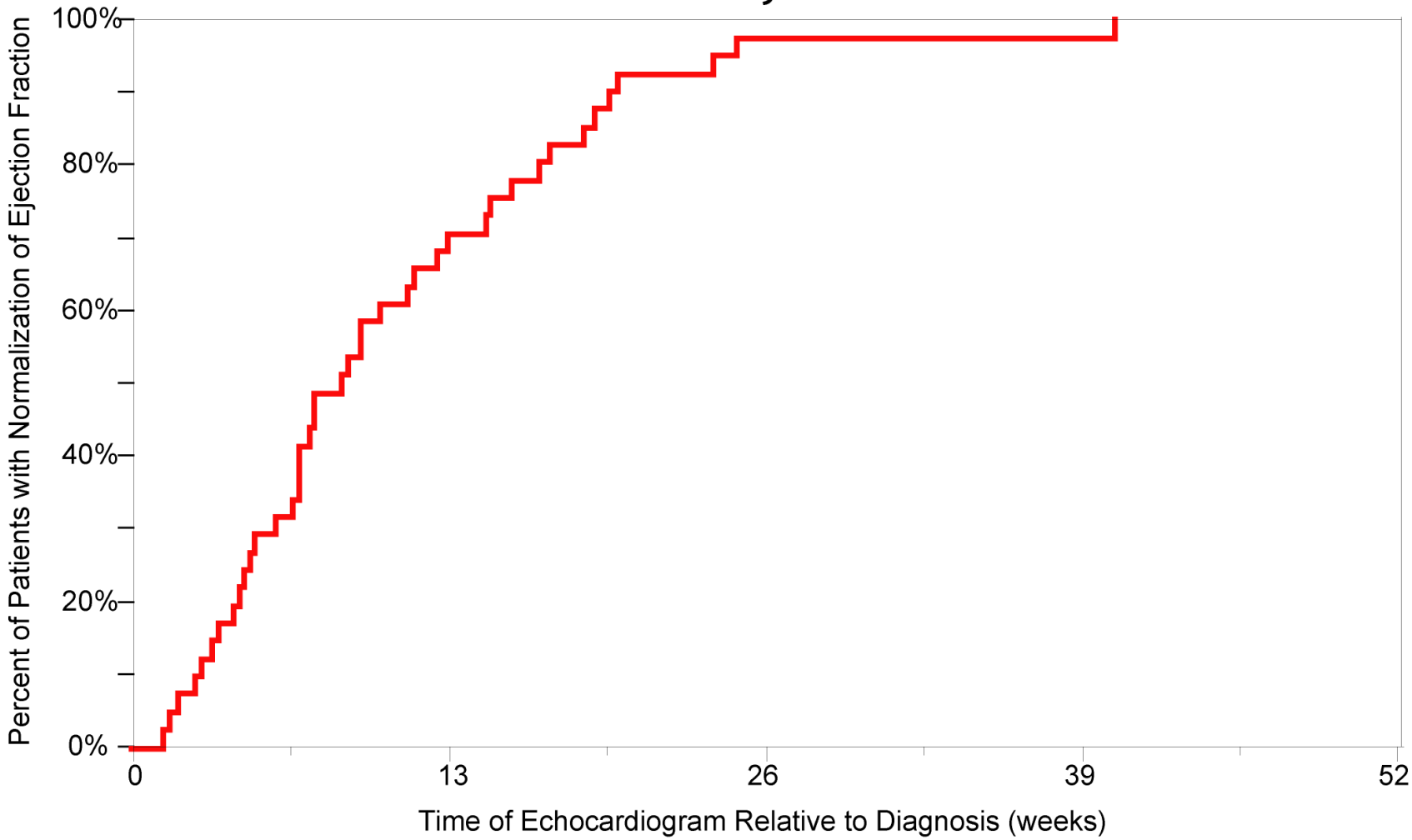
Laboratory Studies

- Variable work-up to date
- However, no reported abnormalities in various markers of inflammation and injury based on reported individual laboratory parameters
  - Troponin-I
  - B-type natriuretic peptide
  - high sensitivity/ultra-sensitive/“regular” C-reactive protein
- Difficulty with standardization of BNP and CRP makes comparison difficult

Echocardiography

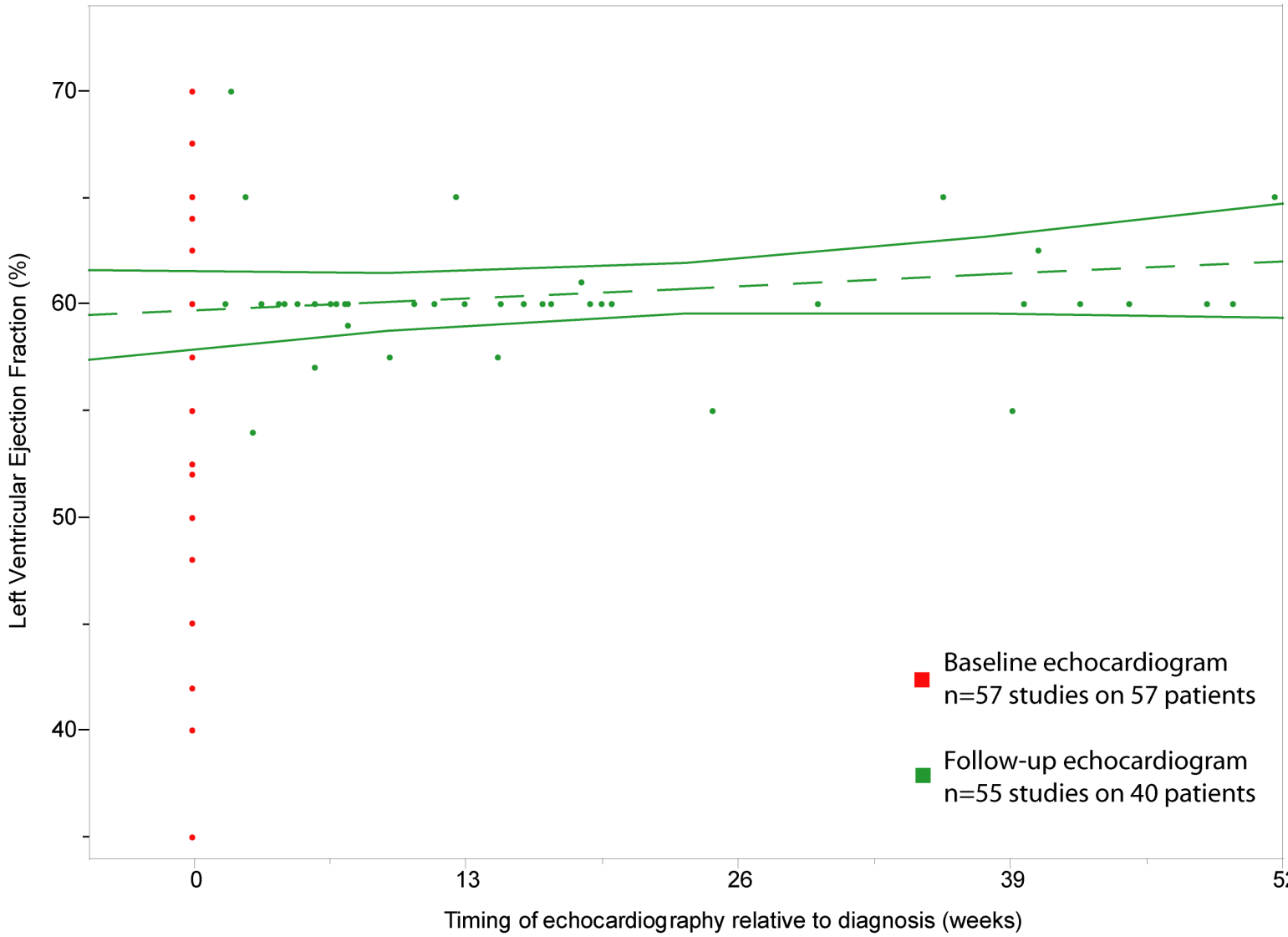
- 57 (85.1%) with echo during acute illness
- Follow-up in 40
  - 11-362 days (median 102 days) after diagnosis
  - LVEF 61±4% (range 54-75%)
  - No evidence of ventricular dilatation, diastolic dysfunction, regional wall motion abnormality, or pericardial effusion

Follow-up of 40 patients and time to normalization of left ventricular ejection fraction



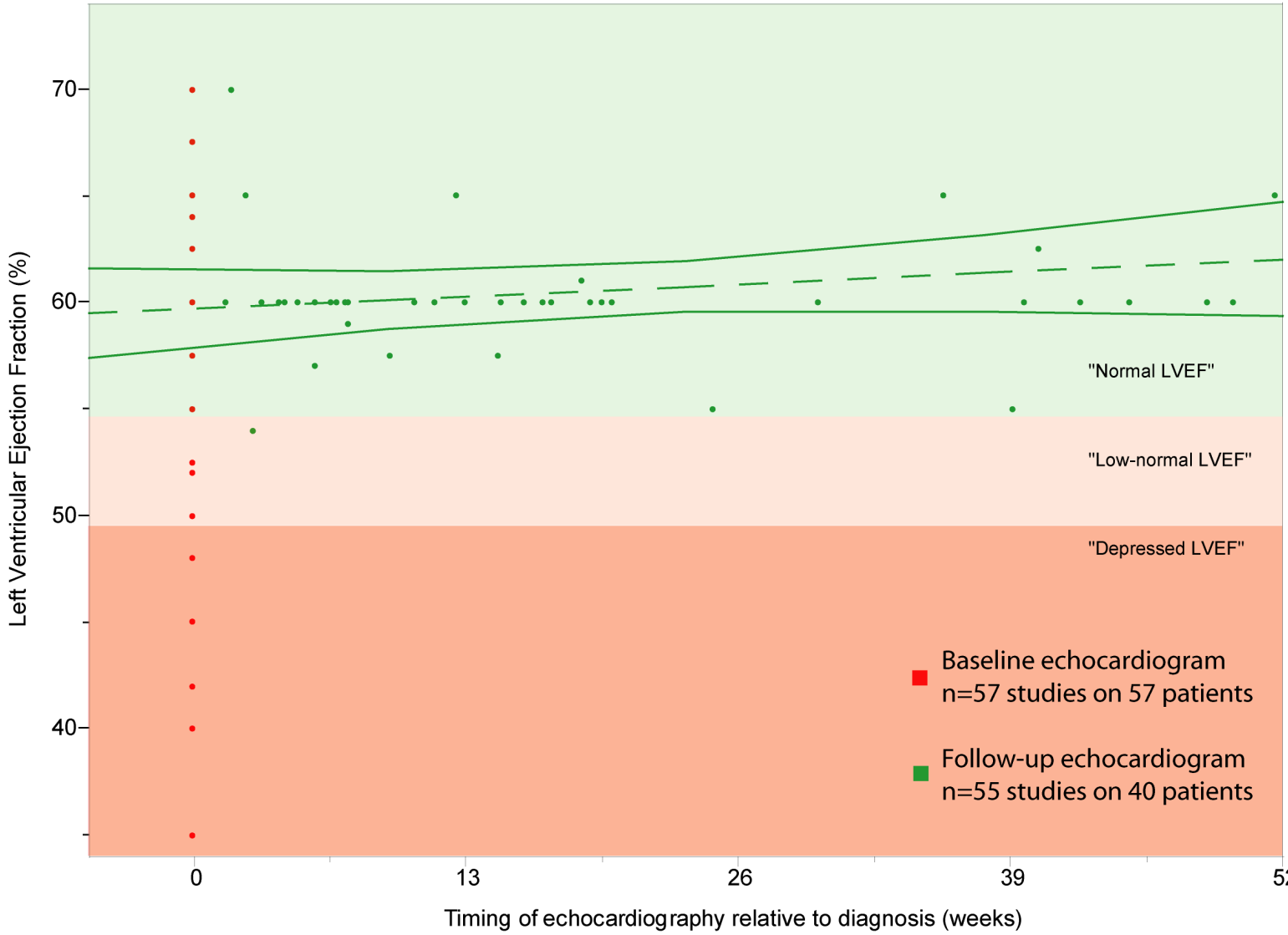
Time of first echocardiogram showing left ventricular ejection fraction of ≥55%. Mean time to normalization of ejection fraction was 10.6±7.9 weeks (median 8.6 weeks). Mean ejection fraction 61±4%. In longer-term follow-up (19.0±15.7 weeks, median 14.6 weeks), the mean ejection fraction was 60±4%.

Recovery of ejection fraction relative to time of echocardiography



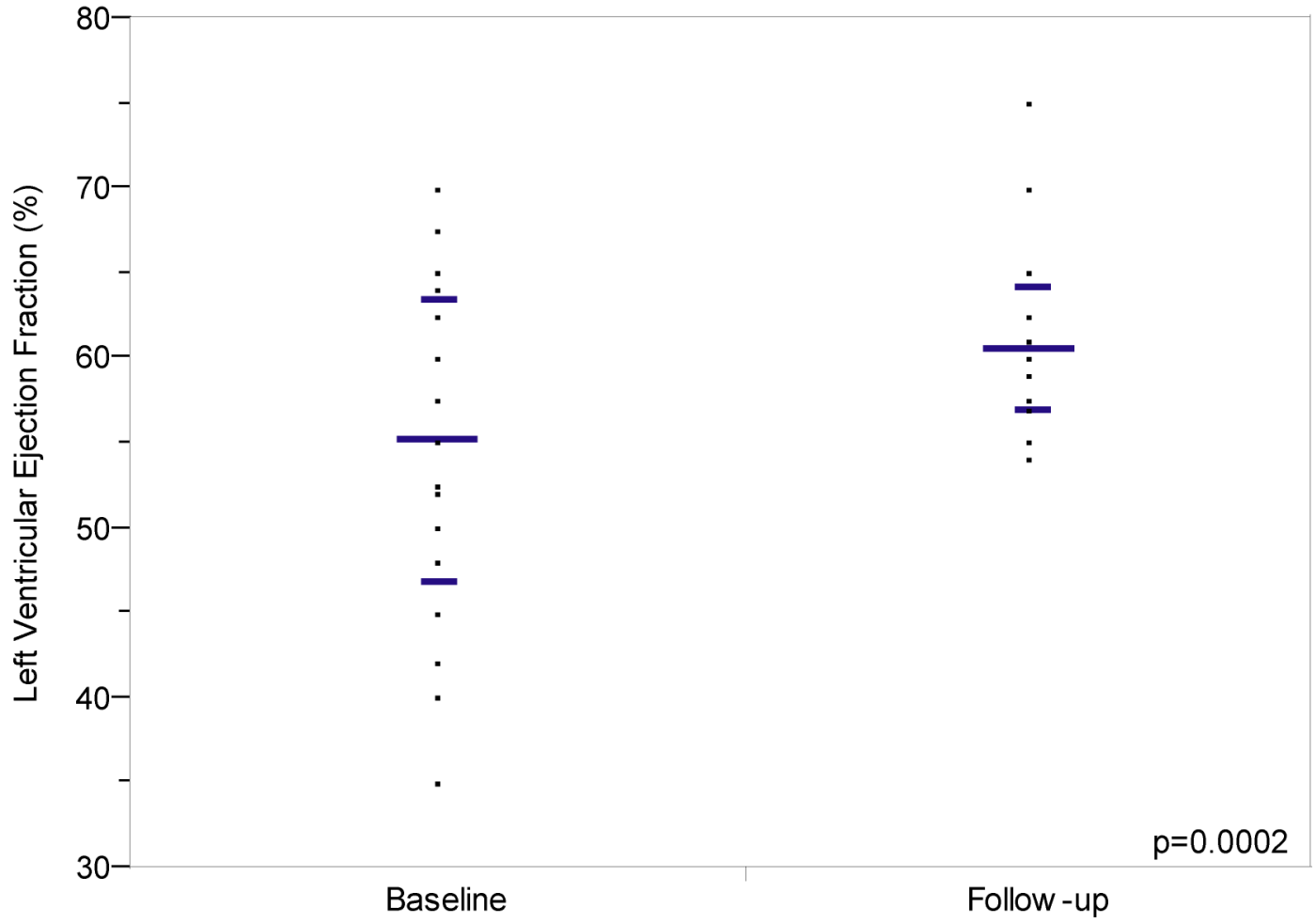
Quantitative evaluation of ejection fraction relative to time of echocardiography since time of diagnosis. Time (0) indicates ejection fraction at time of initial presentation. Dashed line represents linear fit of ejection fraction in follow-up with solid lines representative of 95% confidence interval.

Recovery of ejection fraction relative to time of echocardiography



Quantitative evaluation of ejection fraction relative to time of echocardiography since time of diagnosis. Time (0) indicates ejection fraction at time of initial presentation. Dashed line represents linear fit of ejection fraction in follow-up with solid lines representative of 95% confidence interval.

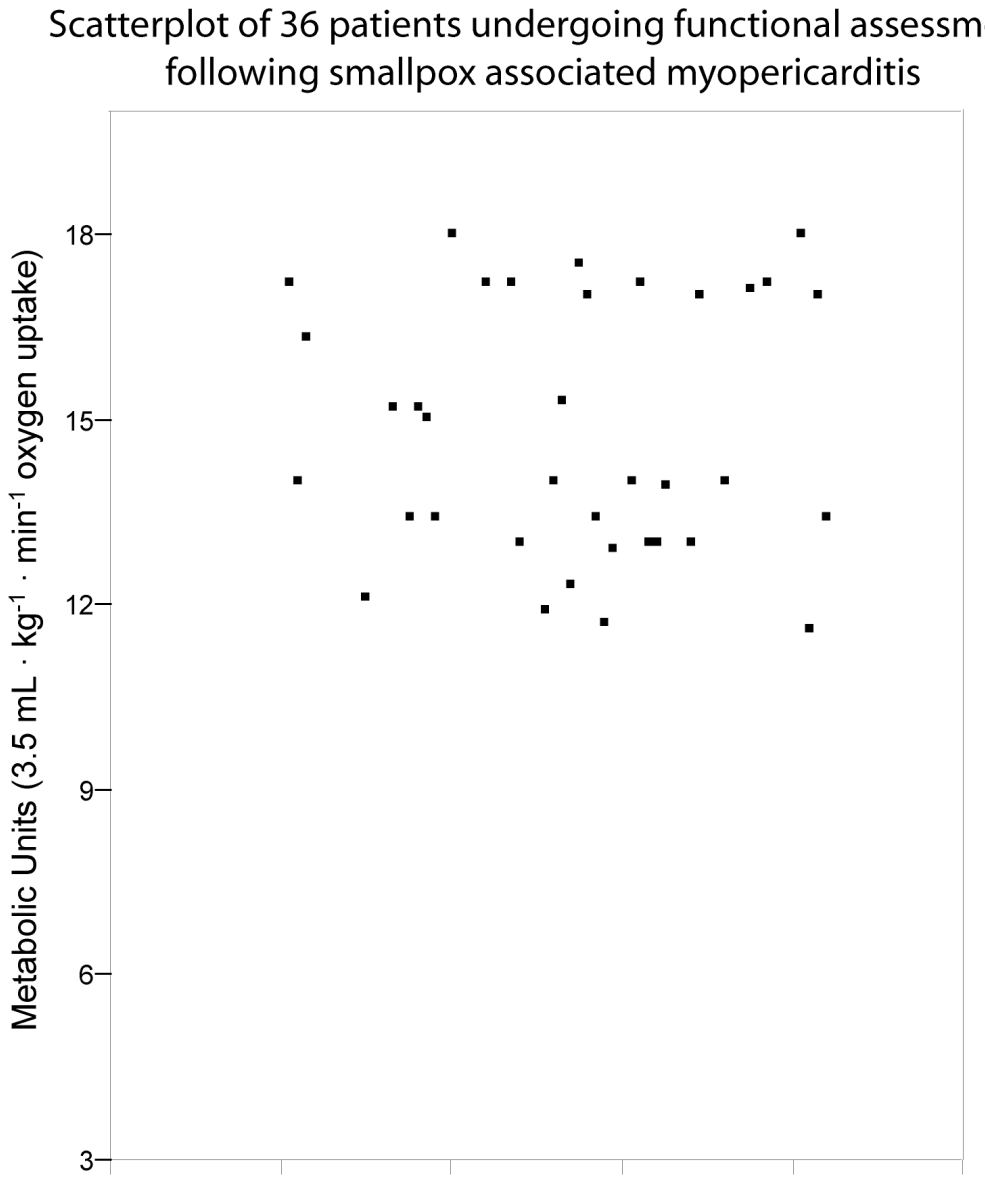
Ejection fraction during initial presentation and at follow-up



Quantitative evaluation of echocardiography stratified by time of presentation (Baseline) or at a mean of 19.0±15.7 weeks (median 14.6 weeks) after diagnosis (Follow-up). Lines represent mean and 95% CI. A statistically significant improvement was noted with a mean ejection fraction of 55±8% to 61±4%.

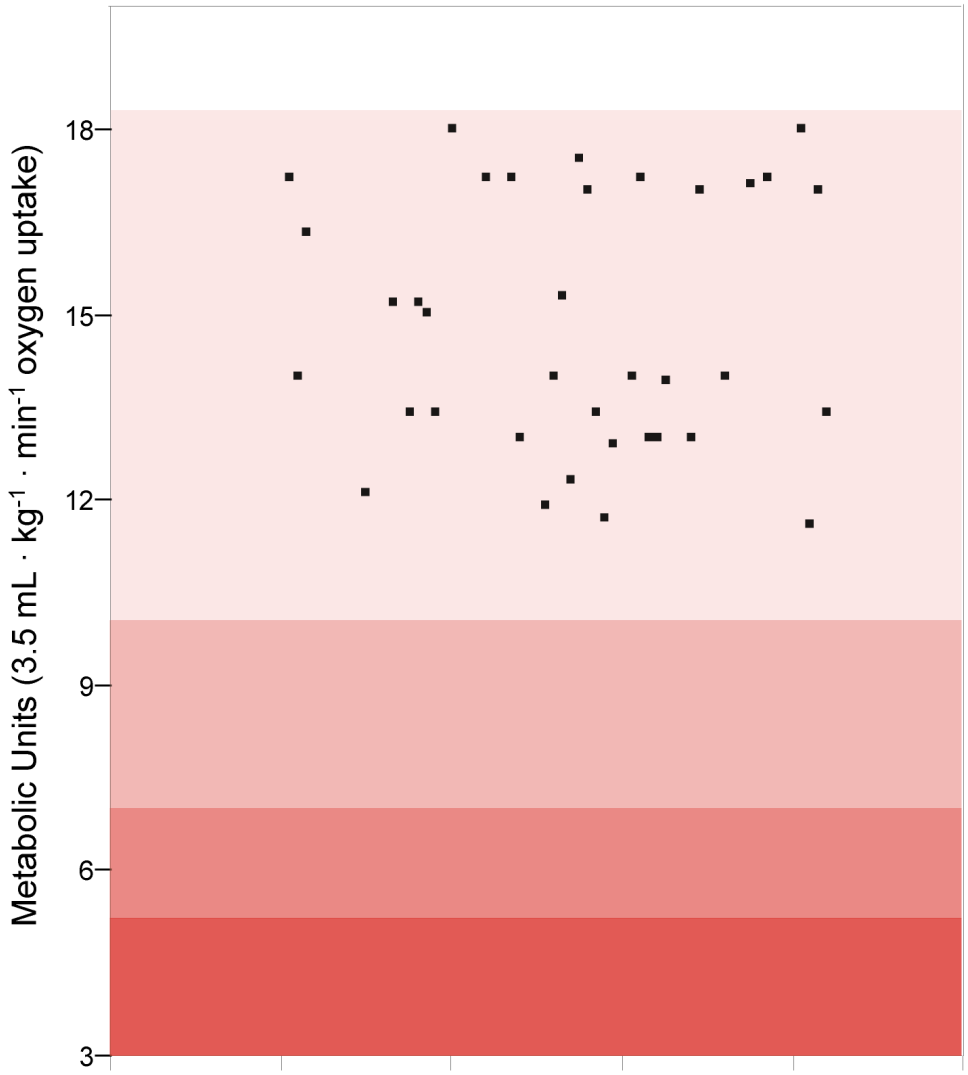
Functional Assessment

- Treadmill testing using Bruce protocol
  - 36 patients at 18-348 days (median 75 days)
  - Exercise duration 12.3±1.8 min (9.0-17.0 minutes)
  - Maximum heart rate 183±10 bpm (95.7±5.8% age adjusted maximum predicted heart rate)
  - Rate-pressure product of 31,031±4,559
- No ECG abnormalities and no cardiac symptoms were provoked



Results of treadmill testing using the Bruce protocol in 36 patients at a mean of 19±14 weeks. Mean exercise duration 12.3±1.8 min (9.0-17.0 minutes) to 95.7±5.8% age-adjusted maximum predicted heart rate.

Scatterplot of 36 patients undergoing functional assessment following smallpox associated myopericarditis



Elite endurance athletes

Running (8 min/mile), stairs with heavy load, boxing

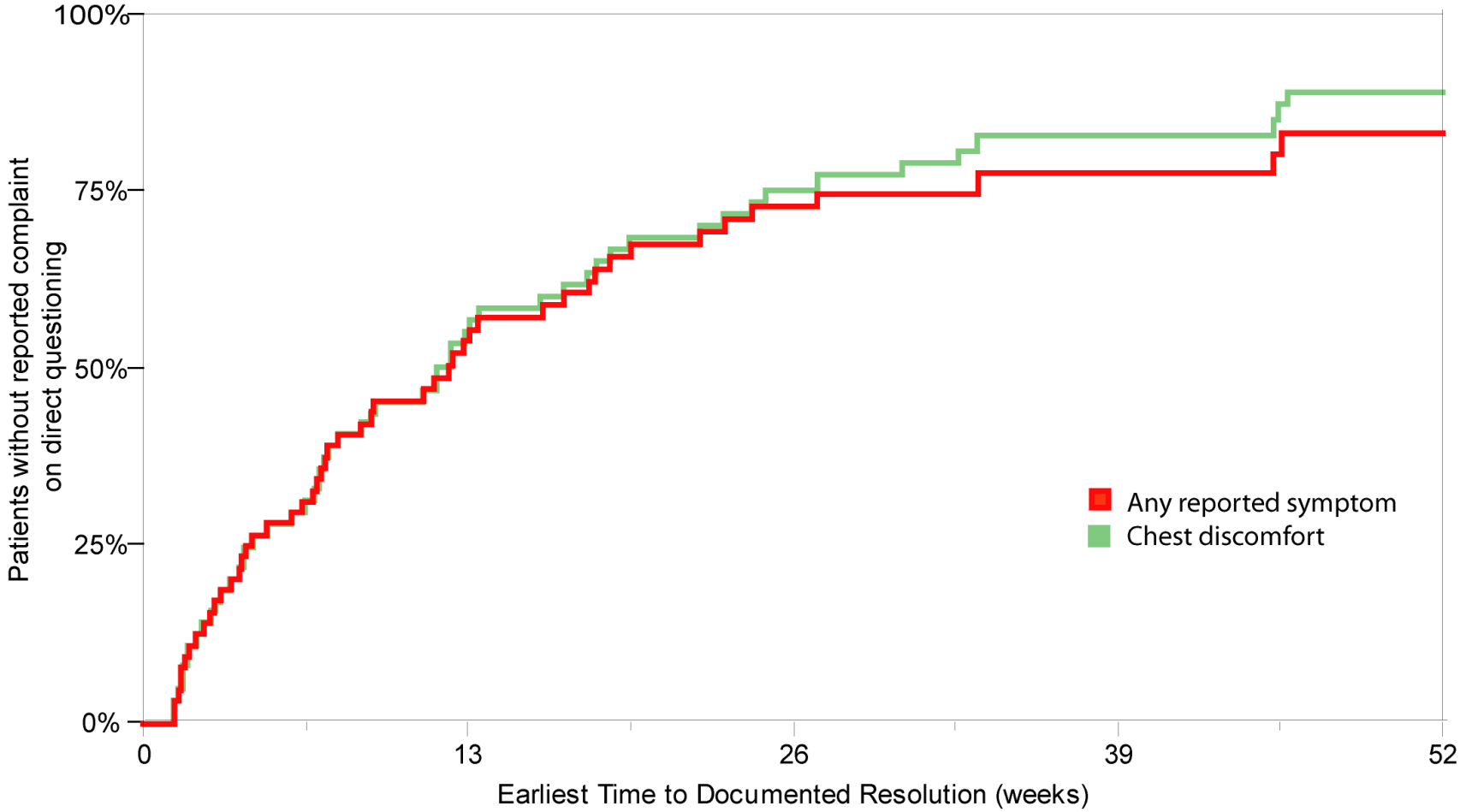
Heavy factory work, running (10 min/mile)

Light factory work, stairs, bicycle riding (10 mph)

Office work, light housework, golf (walking with bag)

Results of treadmill testing using the Bruce protocol in 36 patients at a mean of 19±14 weeks. Mean exercise duration 12.3±1.8 min (9.0-17.0 minutes) to 95.7±5.8% age-adjusted maximum predicted heart rate.

Follow-up of 64 patients with probable or confirmed smallpox associated myopericarditis

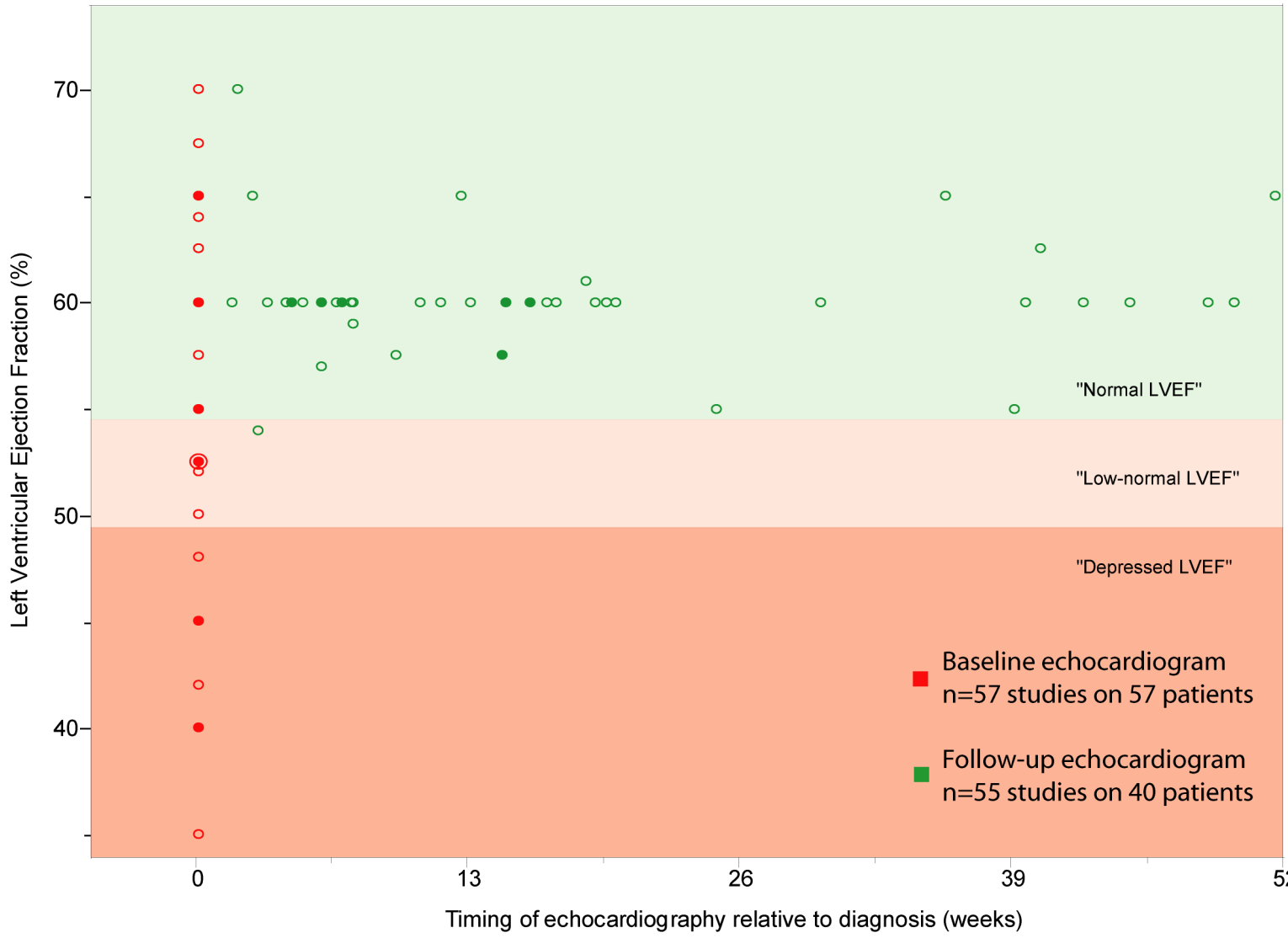


Time to earliest documented resolution of symptoms, recorded at the time of interview by VHC provider (without attempt to determine when symptoms resolution occured). At a mean follow-up of 32±16 weeks in 64 patients; 56 (87.5%) reported complete resolution of any symptom even remotely referable to cardiac disease; 3 (4.5%) reported continued fatigue, and 2 (3.1%) reported headaches, 1(1.6%) reported dyspnea with extreme exertion.

Persistently Symptomatic Patients

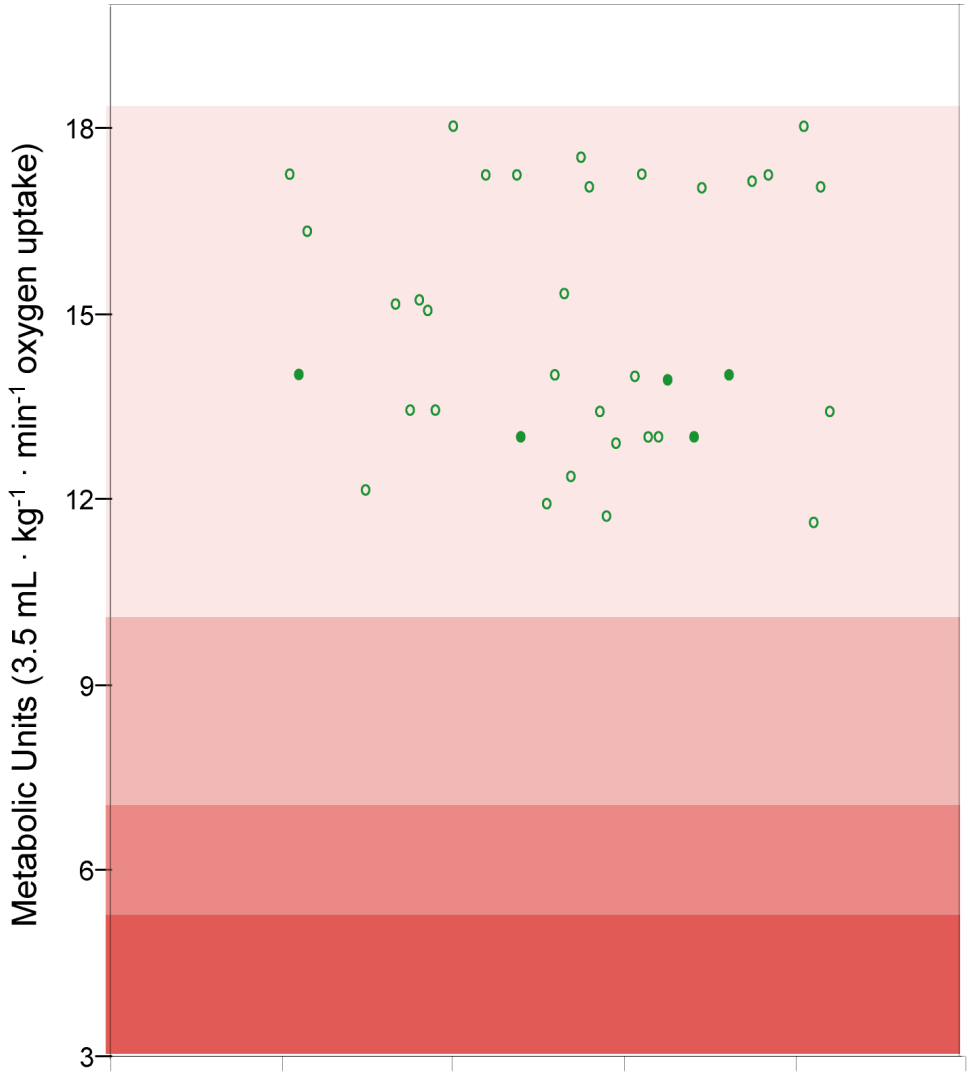
	Full Recovery (n=50)	Continued Symptoms (n=14)
Age, years	27.1±5.6	25.1±3.6
Time from vaccination to evaluation, days	10.4±3.7	10.0±2.0
Weeks to follow-up, mean±SD (median)	30.0±15.6 (33.0)	34.6±15.6 (32.2)
Echocardiography		
Abnormal at presentation	15/43 (34.9%)	8/12 (66.7%)
Ejection fraction at presentation, %	57±8	51±8*
Ejection fraction on follow-up, %	61±4	60±1
Abnormal ECG on presentation	28/46 (61.0%)	7/11 (63.6%)
Peak cardiac isoenzymes, mean±SD (median)		
Creatine kinase (IU/L)	529±360 (404.0)	484±303 (559.0)
CK-MB (ng/dL)	36.0±21.6 (15.3)	31.1±21.7 (20.2)
Troponin-I (ng/dL)	13.6±24.3 (5.4)	17.0±28.8 (7.7)
Treadmill testing		
Percent age-predicted heart rate, %	95.2±4.6	93.6±10.3
Duration, minutes	12.4±1.8	11.3±1.5
Metabolic equivalents, METS	15.0±2.2	13.6±0.5

*p=0.049, otherwise, not statistically significant. Continuous variables expressed as mean±SD. Categorical variables expressed as raw data (percent of column total).



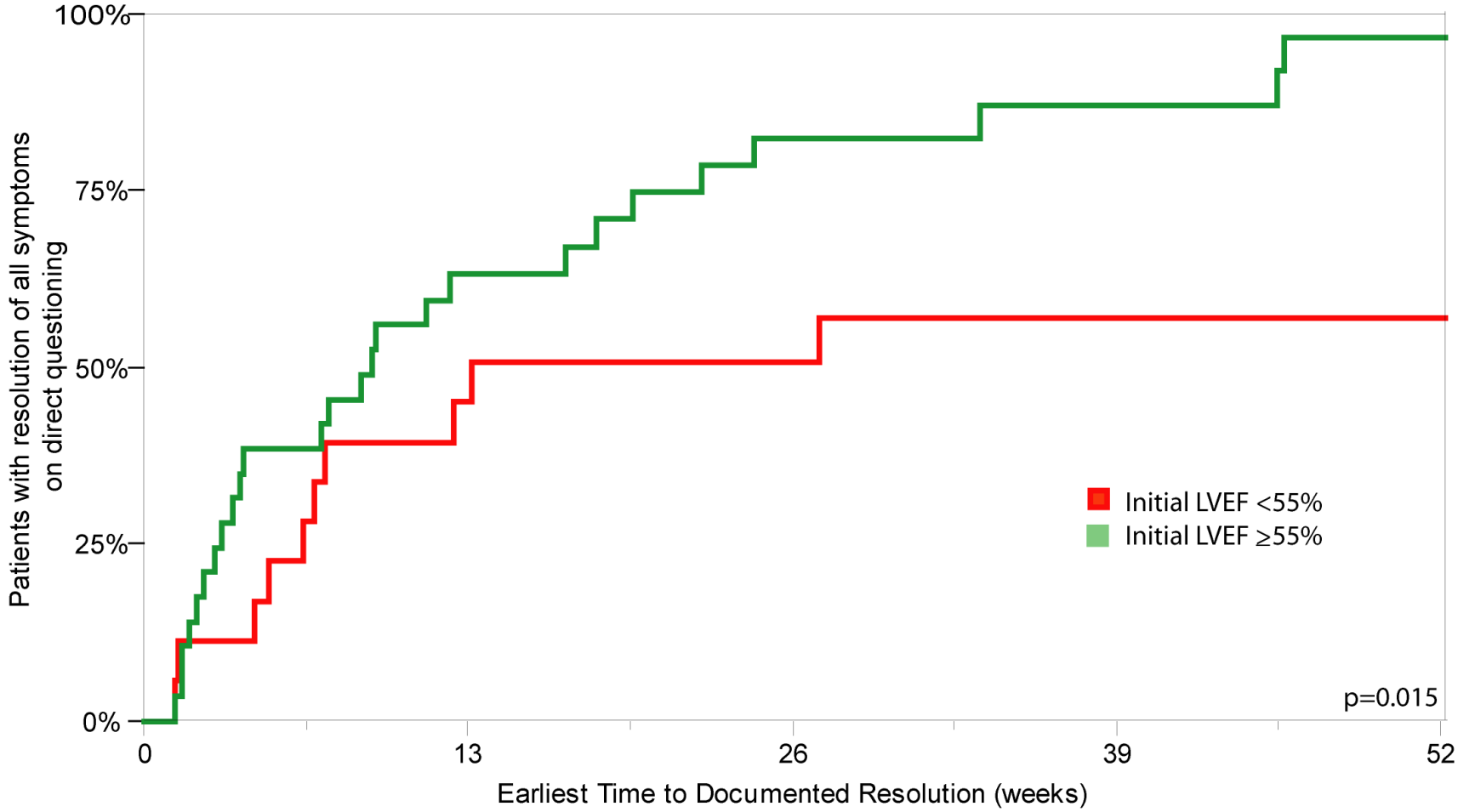
Quantitative evaluation of ejection fraction relative to time of echocardiography since time of diagnosis. Time (0) indicates ejection fraction at time of initial presentation. Filled circles represent those patients reporting persistent symptoms, empty circles represent those with full clinical recovery. For all patients studied with reported continued symptoms, there was documented early normalization of ejection fraction.

Scatterplot of 36 patients undergoing functional assessment following smallpox associated myopericarditis



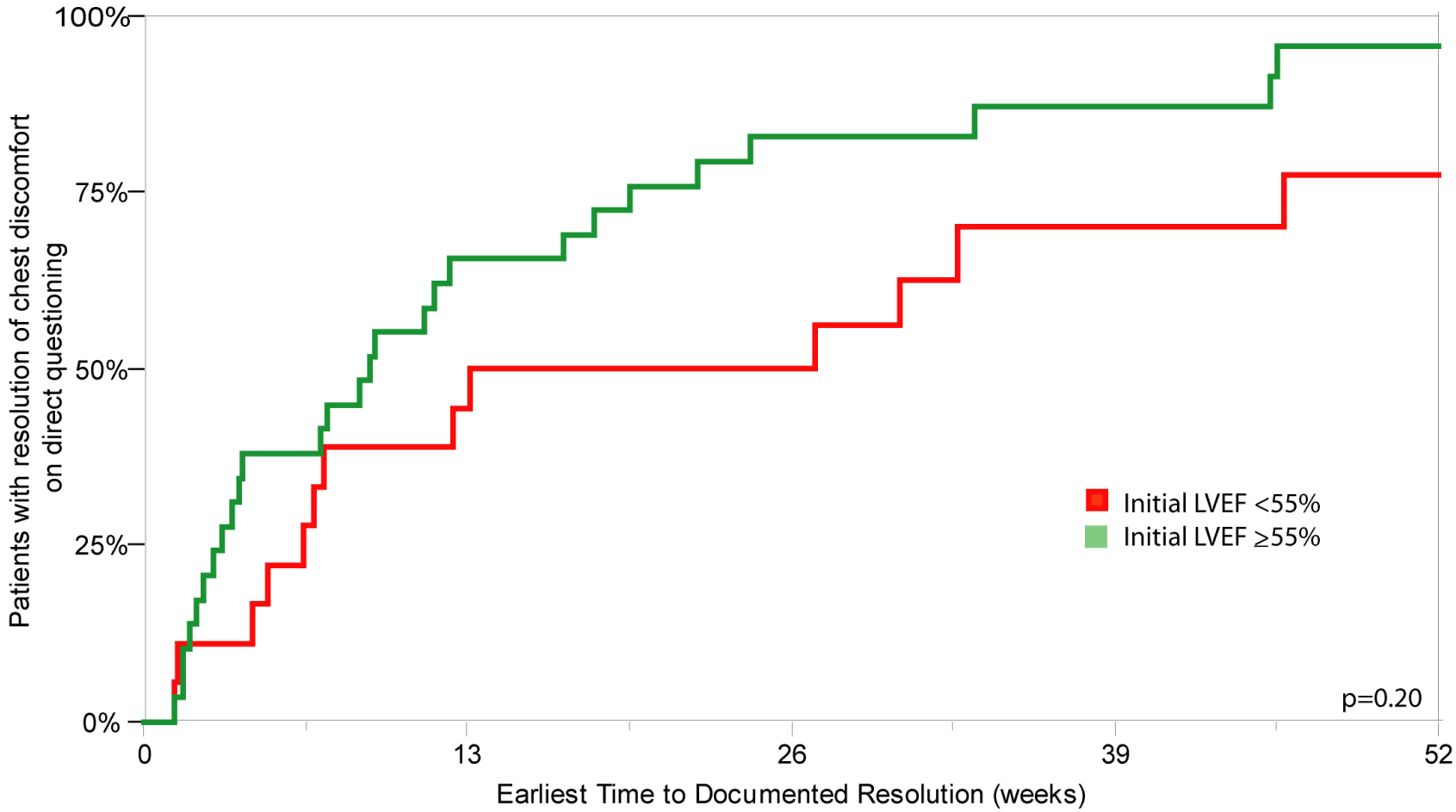
Results of treadmill testing using the Bruce protocol in 36 patients at a mean of 19±14 weeks. Mean exercise duration 12.3±1.8 min (9.0-17.0 minutes) to 95.7±5.8% age-adjusted maximum predicted heart rate. Filled circles represent those with reported persistent symptoms, empty circles represent those reporting full clinical recovery.

Follow-up of 64 patients reporting symptoms stratified by ejection fraction at time of illness



A statistically significant difference in resolution of all symptoms (chest discomfort, headache, fatigue, dyspnea) when stratified by LVEF at time of presentation (using baseline LVEF as surrogate measure of "degree of illness"). Resolution of symptoms 87% vs. 56% (p=0.015) at mean of 32±16 weeks (median 32.7 weeks) after diagnosis for those with preserved LVEF (mean 61±4%) compared to those with depressed LVEF (mean 47±6%) at baseline, respectively.

Follow-up of 64 patients reporting symptoms referable to cardiac disease stratified by ejection fraction at time of illness



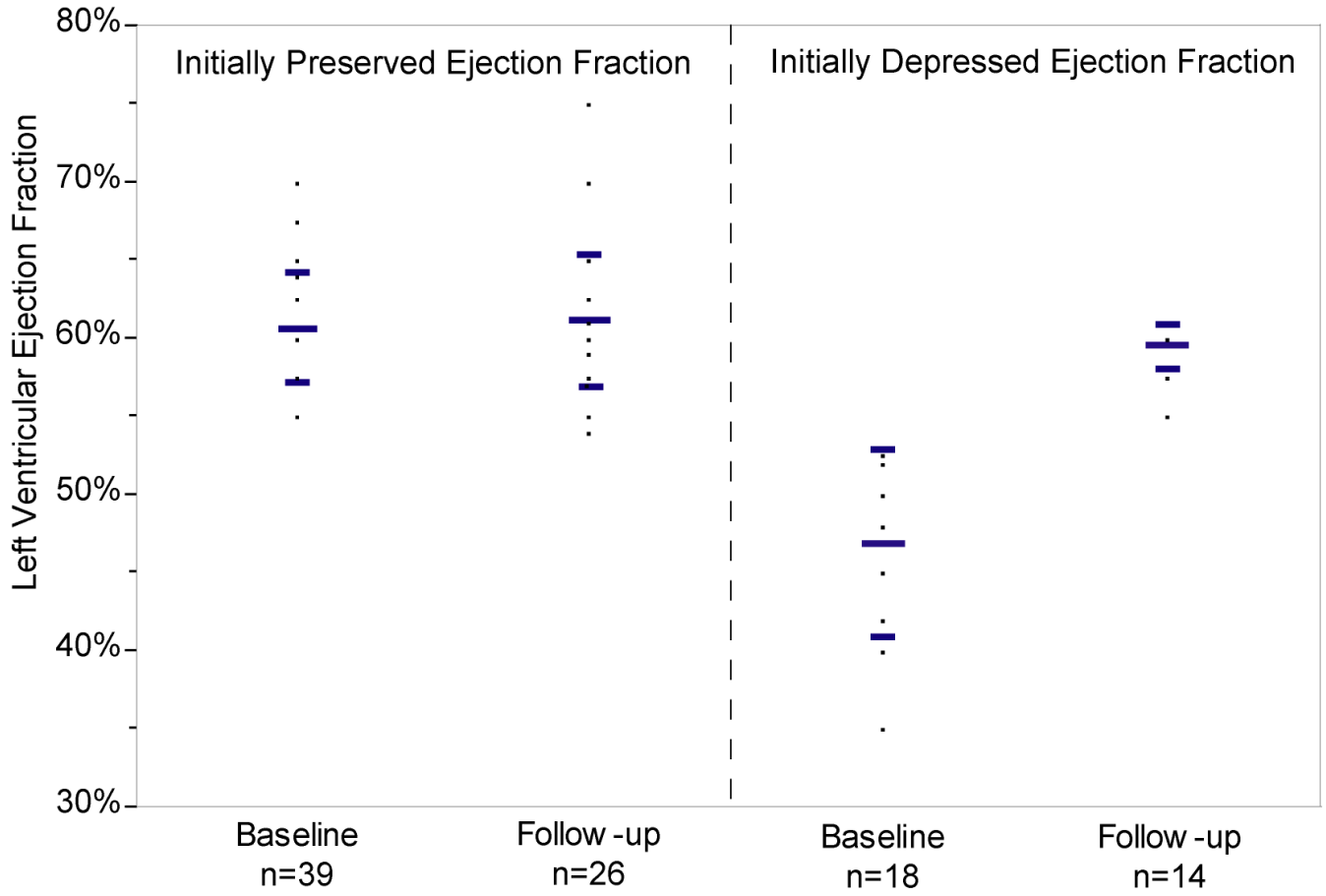
No statistically significant difference in resolution of symptoms referable to cardiac disease when stratified by LVEF at time of presentation (using baseline LVEF as surrogate measure of "degree of illness"). Resolution of chest discomfort 91% vs. 78% (p=0.20) at mean of 32±16 weeks (median 32.7 weeks) after diagnosis for those with preserved LVEF (mean 61±4%) compared to those with depressed LVEF (mean 47±6%) at baseline, respectively.

Follow-up on Patients with Initially Depressed Ejection Fraction

	Initially Depressed (n=18)	Preserved (n=39)	P-value
Initial ejection fraction, %	47±6	61±14	0.01
Peak troponin-I, ng/mL	17.7±23.1	12.3±25.9	0.49
Peak CK, IU/L	566±353	478±343	0.40
Graded exercise testing, minutes	11.6±1.5	12.7±1.8	0.41
Metabolic units	14.5±1.5	15.1±2.2	0.41

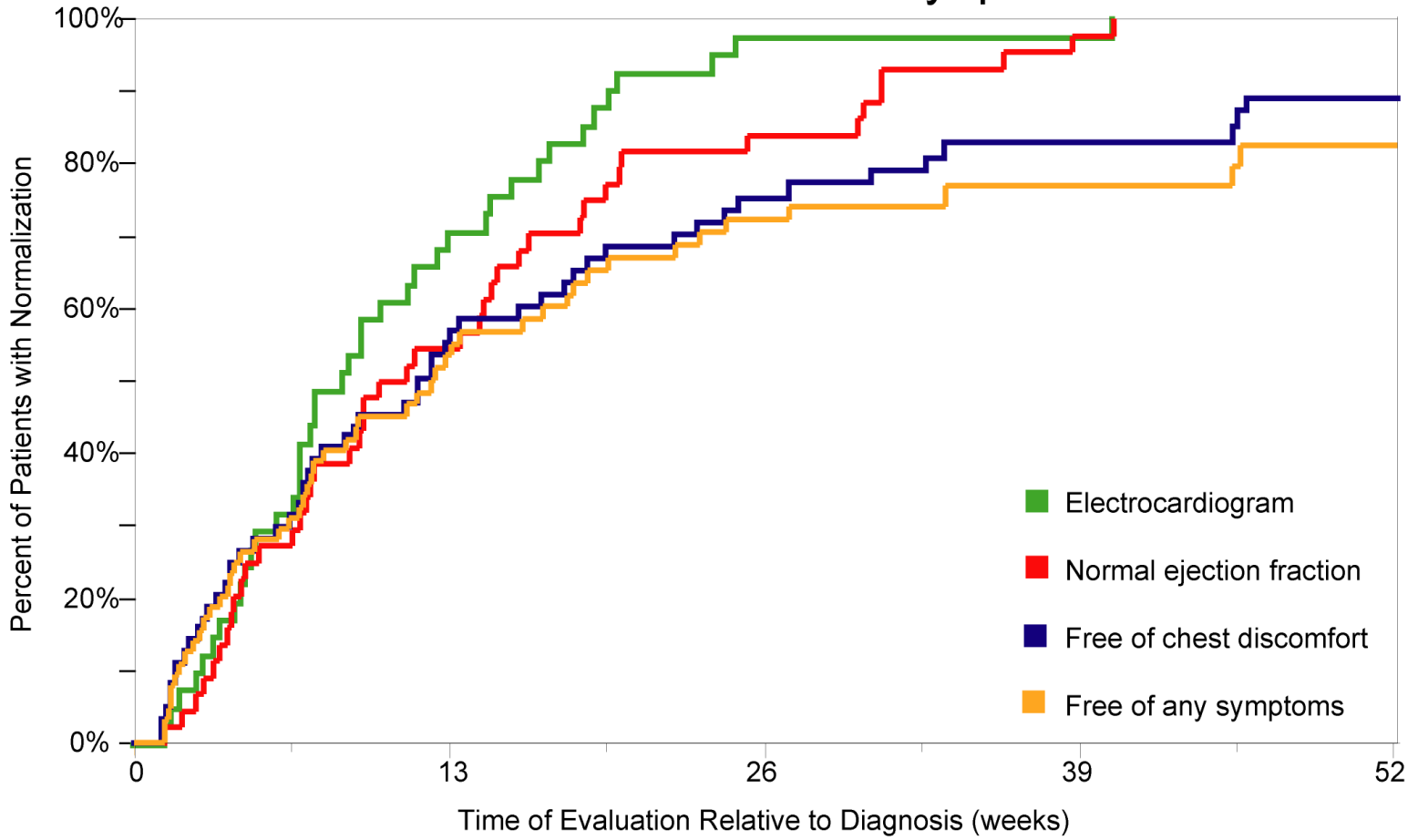
- No change in follow-up exercise capacity.
- More symptomatic on follow-up, but not cardiac symptoms.
- What about normalization of myocardial

Ejection fraction during initial presentation and at follow-up



Quantitative evaluation of echocardiography stratified by time of presentation (Baseline) or at a mean of 19.0±15.7 weeks (median 14.6 weeks) after diagnosis (Follow-up). There was no difference in EF between those with an initially depressed EF at baseline and at follow-up ($p=0.60$). There was a statistically significant improvement in EF in those with an initially depressed EF at baseline and at follow-up ($p<0.0001$). There was no difference in EF at follow-up for those with an initially preserved or depressed EF ($p=0.20$).

Time to documented resolution or normalization of parameters felt to be indicative of recovery in patients after vaccinia-associated myopericarditis



Normalization of either electrocardiography or ejection fraction by echocardiography or resolution of symptoms relative to time of initial presentation. Time of evaluation denotes the time of performance of those studies (ECG or echocardiography) made available for review, or date of VHC provider interview documenting resolution of chest discomfort or any symptoms the patient self-reported as referable to smallpox vaccination (without attempt to note when patient reported resolution).

Conclusions

- Post-vaccinial myopericarditis should be considered in patients with chest pain 30 days following smallpox vaccination
- ECG, echocardiography, and functional status are documented to return to normal within a few months after onset of illness
  - Normal findings on all patients studied following previously recommended 4 to 6 week period of recovery
- ~22% of patients may have persistent subjective complaints
  - 40% of these are not referable to cardiac disease
  - Those with atypical, persistent chest discomfort are without objective functional limitation, and with normal myocardial function

Limitations

- Data for recovery recorded as time of documentation
  - Data presented are “worst-case” scenario

- Cannot exclude alternative etiology to persistence of symptoms
  - “Get better to get deployed”
  - Pre-existing migraine disorder in a case with persistent headache
  - Unquantified symptoms – “fatigue”

Overcoming Limitations

- Need for objectified data
  - Consideration that all patients with post vaccinia cardiac disease be referred to Brooke or Walter Reed AMC for standardized evaluation and follow up
  - VHC has created structured questionnaire for annual follow-up using validated scales for collection of subjective information
  - Annual follow-up, coordinated by VHC for, at a minimum, 2 to 5 years

	Follow-Up Cohort (n=64)	Objective and Clinical Follow-Up Data (n=42)	Clinical Follow-Up Only (n=22)
Age, years	26.6±5.2	27.1±5.6	25.8±4.4
Ethnicity			
Caucasian	60 (89.5%)	39 (92.9%)	20 (90.9%)
African-American	4 (6.0%)	3 (7.2%)	0 (0.0%)
Hispanic	2 (3.0%)	0 (0.0%)	1 (4.6%)
Asian	1 (1.5%)	0 (0.0%)	1 (4.6%)
Vaccination to evaluation, days			
Mean±SD	10.4±3.6	10.5±4.0	10.0±1.9
Median (range)	10 (3-25)	11 (3-25)	10 (7-14)
Initially depressed LVEF	18 (28.1%)	14 (33.3%)	4 (18.2%)
Mean LVEF	55±8	56±8	54±10
Median (range)	58 (35-70)	55 (40-70)	58 (35-65)
Time to follow-up, weeks*			
Mean±SD	31.5±15.2	33.8±15.3	25.6±15.0
Median (range)	32.7 (1.6-58.1)	35.1 (3.6-58.1)	23.9 (1.6-56.1)
Time to resolution of symptoms			
Mean±SD	16.8±15.9	14.6±15.9	20.9±15.5
Median (range)	11.5 (1.3-57.3)	7.4 (1.3-57.3)	14.7 (1.6-56.1)
Persistent Symptoms			
Any reported symptom	14 (21.9%)	6 (14.3%)	8 (36.3%)
Chest discomfort	8 (12.5%)	3 (7.1%)	5 (22.8%)

*p= 0.045, otherwise not significant. Follow-up data collected from 26 different hospitals and clinics from patients in 21 states, and from around the world, some in theaters of war. Many initial cases demonstrated prompt and full clinical recovery, and were discharged from care to fulfill mission requirements. By the time the patient became available for follow-up care, the performance

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	Follow-Up Cohort (n=64)	Objective and Clinical Follow-Up Data (n=42)	Clinical Follow-Up Only (n=22)
Location of Follow-Up			
Civilian	36 (56.3%)	21 (58.3%)	15 (41.7%)
Military	28 (43.8%)	21 (75.0%)	7 (25.0%)
CONUS Medical Center[†]	19 (29.7%)	17 (89.5%)	2 (10.5%)
Other	45 (70.3%)	25 (55.6%)	20 (44.4%)
Branch of Service			
Army	22 (34.4%)	16 (72.7%)	6 (27.3%)
Navy/USMC	9 (14.1%)	3 (33.3%)	6 (66.7%)
USCG/MARAD	18 (28.1%)	13 (72.2%)	5 (27.8%)
USAF	15 (23.4%)	10 (66.7%)	5 (33.3%)
Component of DoD			
Active-Duty	52 (81.3%)	33 (63.5%)	19 (36.5%)
National Guard	5 (7.8%)	4 (80.0%)	1 (20.0%)
Reserve	7 (10.9%)	5 (71.4%)	2 (28.6%)

[†]p=0.01, otherwise not significant. Follow-up data collected from 26 different hospitals and clinics from patients in 21 states, and from around the world, some in theaters of war. Many initial cases demonstrated prompt and full clinical recovery, and were discharged from care to fulfill mission requirements. By the time the patient became available for follow-up care, the performance of these tests was felt to be more of an academic exercise, more than to alter the care of the patient.

	CDC*	DoD	DoD Reality
Myocarditis			
Suspect	Symptoms, PLUS: o ECG changes, or o indeterminate LV dysfunction	Symptoms only o ECG changes, or o indeterminate LV dysfunction	Symptoms only, no cases reported with isolated pathologic ECG changes. Centralized for registry purposes, but excluded from analysis.
Probable	Symptoms, PLUS: o (+) enzymes, or o new LV dysfunction, or o (+) radionuclide imaging	Symptoms, PLUS: o (+) enzymes, or o new LV dysfunction, or o (+) radionuclide imaging	Symptoms, PLUS: o 60 with DOCUMENTED (+) enzymes o 5 with REPORTEDLY (+) enzymes o 0 with NEW LV dysfunction o 0 with (+) radionuclide imaging
Confirmed	Biopsy	Biopsy	4 with biopsy showing inflammatory changes
Pericarditis			
Suspect	Symptoms	Symptoms	Symptoms only, they are centralized for registry purposes, these were excluded from analysis.
Probable	Symptoms, PLUS: o physical exam findings, or o ECG changes, or o echo with fluid	Symptoms, PLUS: o physical exam findings, or o ECG changes, or o echo with fluid	Symptoms, PLUS: o 0 with documented physical exam findings o 2 with ECG changes (1 with DOCUMENTED (-) enzymes, 1 without enzymes drawn) o 6 with echo with effusion (4 with (+) enzymes, 1 with (-) enzymes, 1